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TITLE: Prediction of Acute Mountain Sickness using a Blood-Based Test

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

In the second year we have worked on obtaining IRB approval for Phase II, the validation field work component of the study. As of December 19th 2012 the University of Texas Southwestern Medical School as well as the University of Colorado School of Medicine have approved the protocol. The Human Research Protection Office of the Department of Defense completed initial review and is expected to approve the final protocol in January 2013.
The data collected during Phase I, which was designed to test the concept that an RNA-based gene signature could be used to predict individuals who develop acute mountain sickness and those who do not get sick were very successful. The findings confirm our preliminary analyses and showed that we can successfully predict 9 out of 10 cases of acute mountain sickness and of AMS resistance. In other words, we correctly determined the response in more than 90% of the subjects tested. Phase II of the study is to validate these results in a smaller cohort. As soon as HRPO approval will be final, we will start planning this phase, which will take place in July 2013.

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INTRODUCTION:

The goal of this project is to design an easy-to-use cost-effective test that accurately predicts whether or not someone is likely to develop acute mountain sickness (AMS) when they travel to high altitudes.

BODY:

In this second year we have accomplished most of the task outlined in the statement of work for months 12-24.
We have incurred delays due to the following reasons:

1. longer than anticipated wait for HRPO approval
2. replacement of postdoctoral fellow responsible for the GEXP and gene expression analyses

This means we will be delayed until summer 2013 to do the field study. The team will work in this time frame to complete the analyses of the primary field study, and to write the analysis and report aspects of the second field study so we can catch up quickly.
We have:

- Obtained all IRB approvals for Phase II study IRB materials, with the exception of the last HRPO approval, which is imminent. . This is not in the current milestones and timeline document because the original plan was to have one IRB process for Phase I and Phase II. TATRC human subjects review suggested and we agreed to separate the two phases.
- Started the PAXGene sample collection validation
- Started the GeXP validation
- Started validation and refinement of AMS prediction model
- Started the analysis protein expression alternative model

We anticipate no problems in catching up to our timeline. We have also applied for a no-cost-extension which would extend our timeline to accomplish all milestones at no extra cost for an additional twelve months, to June 2014.

KEY RESEARCH ACCOMPLISHMENTS:

We successfully completed Phase I of the AMS Prediction study. Through prior planning and substantial effort, we were able to start data collection within one week of receiving HRPO final written approval. Over the next 10 weeks we recruited, consented and studied 138 volunteers. We completed the field portion of the study on November 6th, 2011. By November 16th we had selected the subjects who met all inclusion criteria, who completed all aspects of the study, and who either were among the subjects with the most severe AMS score, or were among the group with no symptoms of AMS. On November 17th we submitted the gene expression RNA sample, isolated from the peripheral blood mononuclear cells in each subject, to the UC Microarray Core for analysis. The chips were run and analyzed by December 15th. We then spent about 21 days analyzing the samples to answer the primary question posed by this study: Can we predict from the sea level blood test for RNA signatures who got AMS on the subsequent visit to Breckenridge, Colorado at ~10,000 feet?

The answer is that in 9 out of 10 subjects we have identified a gene signature that predicts their individual resistance or susceptibility to AMS. Before this study, the only way to predict AMS susceptibility was to have previously experienced high altitude. These initial results confirm our initial results showing that RNA-based gene signatures can be used to predict subsequent AMS susceptibility/resistance. The task ahead is to understand the meaning of individual gene components of the signature, and refine the design of the validation study to take place in summer 2013.

REPORTABLE OUTCOMES:

Though the initial results are exciting, and verify our original hypothesis, it is premature to proclaim complete success. Today it is accepted practice to validate gene expression findings in an independent cohort before relying on the validity of a gene expression screening test. That is our current plan, which will be largely complete in 2013, with final analysis and manuscript writing in late 2013 into early 2014.

CONCLUSION:

If the Phase II validation study confirms these findings, we are on track to develop a method for predicting risk of AMS in sea level residents. This was the overarching goal of the entire project, and at this phase, at the end of Year 2, we have achieved as much success as we could hope for by achieving each milestone and also in identifying a gene signature that has potential to change the way we manage risk in people who have never before gone to high altitude.